21. (new) The method of claim 1, wherein the parathyroid hormone is administered in an intermittent fashion.

22. (new) The method of claim 5, wherein the parathyroid hormone is administered in an intermittent fashion.

23 ~~24.~~ (new) The method of claim 21, wherein the parathyroid hormone is administered in an intermittent fashion.

Remarks

The Examiner objected to typographical errors in the specification. Applicants have amended the specification to correct for typographical errors and matters of form.

The Examiner rejected claims 6-14 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable a method of contacting osteoblast cells with a test compound in an *in vivo* murine animal model. In essence, the Examiner asserts that the specification does not teach how to contact osteoblasts with either a glucocoriticoid or a test compound in an intact mouse, as opposed to how to contact osteoblasts in an in vitro model or a SAMP6 or SAMR1 mouse. Applicants respectfully disagree.

As discussed in the "W" article listed on the Examiner's PTO Form 892 (Jilka R.L. et al. Journal of Clinical Investigation 97(7): 1732-1740, 1996)), SAMP6 and SAMR1 mice are models of early senecense that exhibit ostepenia. "The SAMP6 strain as well as the 'normal' control strain SAMR1 were developed over the past 20 yr by investigators at Kyoto University by brother-sister mating of AKR/J mice for > 50 generations. When reared under a specific pathogen-free conditions, SAMP6 exhibit normal incidence of tumors and other specific

abnormalities. Thus, the confounding effects of age-related diseases of inbred mice do not account for either the rapid aging or the osteopenia of SAMP6 mice." See p. 1733.

As discussed in the abstract of the article, at 1 month of age, the number of osteoblast progenitors in SAMP6 marrow was indistinguishable from controls; however, a three-fold decrease was found at 3-4 months of age. Impaired osteoblast formation was temporarily associated with decreased bone formation and decrease bone mineral density, as determined by histomorphometric analysis of tetracyclin-labeled cancellous bone and dual energy x-ray absorptiometry, respectively.

Clearly, SAMP6 and SAMR1 mice are osteoblast-deficient, but not osteoblast knock-out, models. Applicants have shown in Examples 4-6 that a PTH fragment can be used to inhibit the apoptosis of osteoblasts in these osteoblast-deprived models. The Examiner has not presented *prima facie* evidence to support the Examiner's contention that the PTH fragment would not exhibit a similar effect in other bone-containing hosts.

While the Examiner suggests that physical and physiological interactions related to administration of the compound could have an unpredictable effect on the compound of interest, the Examiner does not explain how it would be "incredible" under the PTO guidelines to accept that the invention can be carried out in bone-containing hosts other than SAMP6 and SAMR1 mice, which are accepted models of aging hosts.

The Examiner cites Cornish et al. as prior art which shows that subcutaneous injection of 4 μg of PTH in mice for five days caused catabolic and anabolic effects on bone. Based on this prior art, the Examiner concluded that undue experimentation would be necessary to practice the invention as presently claimed. In the Cornish article, the 4 micrograms per day of the entire PTH protein was administered. In the present specification p. 29, lines 14-16; p. 31, lines 12-13

discloses treating mice with 400 ng/g body weight of a small bovine or human PTH fragment, respectively, daily over a four week period. More generally, the specification teaches that 10 to 1000 micrograms per kilogram body weight be used in each dosage. This limitation has now been added to independent claim 1. Administration of this fragment at the specified concentration resulted in increased bone mineral density in the hindlimbs of the mice. (See specification p. 29 line 19 through p. 30, line 2; p. 31, lines 19-21). Thus, the present application discloses a method which is substantially different from that in Cornish et al. Because the present specification discloses specific guidance and direction to practice the invention, the disclosure is enabling and the rejection to claims 6-14 should be withdrawn.

Furthermore, Examples 5 and 6 are working examples of how to practice the claimed invention in mice. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP § 2164.01(b) citing In re Fisher, 427 F.2d 833, 839 (C.C.P.A. 1970). A person of ordinary skill in the art would find a correlation between the effects of PTH observed *in vitro* and the similar effects observed after *in vivo* administration. Because the specification discloses working examples with a reasonable correlation to the entire scope of the claim, the disclosure is enabling.

The Examiner also supports his conclusion of nonenablement on the unpredictable state of the art and the breath of the claims. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. Without addressing the degree of unpredictability in the state of the art, Applicants have disclosed working examples describing how to practice the invention as claimed in intact mice. Examples 5 and 6 provide detailed procedures on the concentration and route of

administration of PTH in mice to screen for compounds that stimulate bone formation. Because Examples 5 and 6 provide detailed information on how to practice the invention in intact mice, the specification provides sufficient guidance and direction to compensate for any degree of unpredictability in the state of the art, and therefore, the rejection of claims 6-14 should be withdrawn.

If the art is such that a particular model is recognized as correlating to a specific condition (i.e., aging), then it should be accepted as correlative. MPEP § 2164.02. It is widely accepted that effects on primary cultures are correlated with similar effects *in vivo*. In Example 8, primary cultures of osteoblasts were isolated from neonatal murine calavaria and PTH was added directly to the cultures. The results seen in the *in vivo* model were also seen in the *in vitro* model. Indeed, it is known in the art that osteoblasts and osteoclasts possess PTH receptors. Dempster et al. Endocrin. Rev. 14:690-691 (1993). Because osteoblasts possess PTH receptors, they are able to bind PTH *in vivo* as well as *in vitro*. Therefore, Example 8 establishes that osteoblasts respond to PTH both *in vivo* and *in vitro*, and osteoblasts are contacted by PTH *in vivo*. Because one skilled in the art would accept the *in vitro* data as correlating to the *in vivo* data, the specification is enabling for claims 6-14.

Lastly, the Examiner supports his conclusion of nonenablement based on the breadth of the claims. The specification need not disclose everything necessary to practice the claimed invention. What is well-known is best omitted from the specification. In re Buchner, 929 F.2d 660, 661 (Fed. Cir. 1991). Applicants have disclosed in the specification detailed methodologies to practice the claimed invention in cultured cells and in intact mice. Given the level of skill and knowledge in the field, a person of ordinary skill in the field would be able to practice the invention as claimed without undue experimentation. One skilled in the field would know that

the invention as claimed would apply to mammals in general and even vertebrates collectively. Mice have routinely been used as biological models of humans, and the use of a mouse model is reasonably correlated with many if not all mammals based on the substantial similarity in physiology. Because the scope of the enablement bears a reasonable correlation to the scope of the claims, the specification is enabling and the rejection of claims 6-14 should be withdrawn.

The Examiner rejected claims 1-5 under 35 U.S.C. § 112 as being indefinite in their recitation of human parathyroid hormone [hPTH(1-34)]. The Examiner points out that it is unclear from this format whether there are many isoforms of human parathyroid hormone. It is known in the art that terms "human parathyroid hormone [hPTH(1-34)]" and "bovine parathyroid hormone [bPTH(1-34)]" refer to synthetic amino-terminal fragments containing the numbered amino acids of the respective hormones. See Tam, C.S. et al. Endocrinology 110:506-512 (1992); Reeve, J. et al. British Med. J. 280:1333-1390 (1980).

The Examiner suggests that the specification discloses only human parathyroid hormone. Applicants point out that Example 2 beginning on page 22 of the specification discloses the use of bovine parathyroid hormone in *in vitro* assays. (See page 23, line 1 of the specification.) Additionally, Example 5 beginning on page 29 of the specification discloses the use of bovine parathyroid hormone in *in vivo* assays. (See line 15, page 29.)

Applicants have amended claim 1 as suggested by the Examiner. In particular, Applicants have deleted "a therapeutic dose" and inserted --therapeutically effective dosages of between aproximately 10 and 1,000 micrograms per kilogram body weight of isolated parathyroid fragment wherein said parathyroid fragment is--in place thereof. Additionally, Applicants amended claim 1 by deleting "human" before parathyroid hormone; and inserting --(1-34)-- after parathyroid hormone; deleting "reducing the number of osteoblasts undergoing

apoptosis in an individual"; inserting --increasing the lifespan of osteoblasts in a bone-containing host-- in place thereof; deleting "individual" and inserting --host-- in place thereof.

Applicants have similarly amended claim 5 by deleting "human", deleting "[hPTH(1-34)]" and inserting --fragment-- after hormone. Applicants further amended claim 5 by deleting "[hPTH(1-34)]" and deleting "administered in a dose from about 10 μg/kg to about 1000 μg/kg".

The Examiner rejected claims 1-5 as indefinite based on the recitation of "individual" because it was unclear whether individual referred to an animal, tissue, organ, or cell. As mentioned above, Applicants have amended claim 1-3 by deleting "individual" and inserting --bone-containing host-- in place thereof. Claim 4 and 5 depend for claim 1, and therefore the amendment of claim one obviates the indefiniteness of claims 4 and 5.

The Examiner rejected claims 1-5 as indefinite based on the recitation of "such treatment" lacking an antecedent. Applicants have amended claim 1 by deleting "such treatment" and inserting --preventing bone loss or stimulating bone formation-- in place thereof. Support for this amendment is found in the specification on page 8, lines 7-11 and page 16, lines 1-2. Because claims 2-5 depend from claim 1, the amendment of claim 1 addresses the Examiner's rejection of these claims.

The Examiner rejected claim 3 as indefinite based on the recitation of "previously" because it was unclear what time period "previously" encompassed. Applicants have deleted "previously treated with one or more glucocorticoid compounds" in claim 3 and inserted --experiencing adverse bone effects resulting from contact with one or more glucocorticoid compounds.--. Support for this amendment is found in the specification on page 5, line 1 through page 6, line 4.

Applicants have amended claim 4 by deleting "inhallation" and inserting --inhalation-- in place thereof.

The Examiner rejected claims 7, 12, and 13 as indefinite based on the recitation of "said contacting ... is selected from the group consisting of *in vitro* osteoblasts and an *in vivo* murine animal model." because *in vitro* osteoblast cells and *in vivo* murine animal are not species of "contacting." Applicants have amended claim 7 to depend from new claim 17, deleted "is selected from the group consisting of *in vitro* osteoblast cells and an", inserted --occurs--, and inserted --in a--. The deletion of the Markush language from claim 7 removes any indefiniteness because there is no longer a group with a species.

Applicants have amended claim 12 by inserting --glucocorticoid-treated--, inserting --occurs in vitro--, and deleting "is selected from the group consisting of *in vitro* osteoblast cells and an *in vivo* murine animal model". As with claim 7, the deletion of the Markush language from claim 12 obviates the Examiner's rejection based on indefiniteness because there is no group in the claims, and therefore, no species.

Applicants have added new claims 17 and 19 to separate the claims written on the *in vitro* and *in vivo* assays as suggested by the Examiner. Applicants have amended claim 13 to depend from claim 19. Because claim 13 depends from claim 19 which has no Markush group, claim 13 is no longer indefinite.

The Examiner rejected claims 7 and 8 as indefinite because the claims read on both an *in vitro* and *in vivo* assay method. As discussed above, Applicants have amended claim 7 to depend from new claim 17. The amended claim 7 reads only on *in vivo* assays. Because claim 8 depends from amended claim 7, claim 8 now reads only on *in vivo* assays. Because claims 7 and

8 have been amended to read only on *in vivo* assays and not on both *in vivo* and *in vitro* assays, the rejection of these claims based on indefiniteness should be withdrawn.

The Examiner concluded that Applicants' claim to "*in vivo* assays" which use *ex vivo* histomorphology to determine bone changes in an animal model were are indefinite because *ex vivo* methods by definition occur outside the scope of *in vivo* methods. Applicants point out that amended claim 7, amended claim 9, and new claim 17 are directed to a method of screening for compounds that stimulate bone formation. The claims incorporate both *in vivo* and *ex vivo* elements. Thus, these claims are improperly characterized as exclusively *in vivo*. Furthermore, Applicants assert that method claims are not rendered indefinite simply because they incorporate *in vivo* and *ex vivo* steps. Therefore, the rejection of the claims 7-8 based on indefiniteness should be withdrawn.

The Examiner rejected claims 12 and 13 as indefinite because they read on both *in vitro* and *in vivo* assays. As discussed previously, Applicants have amended claim 12 to be directed to *in vitro* assays and added claim 19 direct to *in vivo* assays. Claim 13 was amended to depend from claim 19 and is therefore directed to *in vivo* assays. The Examiner also rejected claims 12 and 13 as indefinite because the specification teaches *ex vivo* methods for determining bone changes and Applicants claim *in vivo* assays. As explained previously, the Examiner's objection based on indefiniteness resulting from the use of *ex vivo* histomorphometry methods to determine the effect on bones should be withdrawn because a method claim that incorporates *in vivo* and *ex vivo* steps are not per se indefinite. Therefore, the rejections of claims 12 and 13 should be withdrawn.

The Examiner rejected claim 9 because there is no antecedent basis for "said murine animal model." Applicants have amended claim 9 to depend from claim 7. Claim 7 depends

form claim 21 which provides the antecedent basis for "said murine animal model." Applicants further amended claim 9 by inserting --further comprising, confirming--; deleting "wherein said" and "is confirmed by" and inserting --using--.

The Examiner rejected claims 10 and 14 as indefinite in their recitation of "said determination of apoptotic cells is selected from the group consisting of microscopy of stained cells, TUNEL, Hoescht 33258 dye, and video image analysis." because "microscopy of ... analysis" are not species of "determination". Applicants have amended claims 10 and 14 by deleting "said determination of", inserting --are identified using a technique--, deleting "is", and inserting --analysis-- before "Hoescht" and "and video". Microscopy of stained cells, TUNEL analysis, Hoescht 33258 dye analysis, and video image analysis are all species of technique; therefore, as amended, claims 10 and 14 are not indefinite.

The Examiner rejected claims 11-14 as indefinite in their recitation of "said osteoblastic cells" because it is unclear whether these cells are pre-glucocorticoid treated cells. Applicants have amended claim 11 and claim 12 by inserting --glucocorticoid-treated-- after "said." As amended, claims 11 and dependent claims 12 and 14 are not indefinite. Amended claim 13 depends from new claim 19.

The Examiner rejected claims 6, 9 and 10 under 35 U.S.C. § 102(b) as being anticipated by Hill et al. (1997). Applicants have amended claim 6 by inserting--wherein the osteoblast cells are selected from MYLO-Y$, MC3T3-E1, MG-63, or other immortalized osteoblast cell line-- in step (a); deleting "said" in step (b); inserting --treated cells that are-- and --untreated-- in step (c); and deleting "cells", "that have not been contacted with said compound, wherein fewer apoptotic cells following contact with said compound than in the absence of said contact indicates that said compound inhibits apoptosis resulting in stimulation of bone formation" in

step (c). Support for the the additional limitation that the osteoblastic cells are MLO-Y4, MC3T3-E1, MG-63, or other immortalized osteoblast cell lines is found in the specification at page 23, line 6 and page 40, lines 7-8. As the Examiner is aware, to anticipate a claim, the reference must teach every element of the claim. Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987) cert. denied, 484 U.S. 827 (1987). Because Hill et al. does not teach an assay using osteoblast cell lines, it does not anticipate claims 6. Additionally, applicants have amended claim 9 to depend from claim 7 directed to an *in vivo* assay system. Hill et al. does not teach an *in vivo* assay, and therefore, does not anticipate claim 9. Claim 10 depends from claim 6 which was amended as described above. Because claim 10 encompasses the limitations of claim 6, and because claim 6 contains limitations not disclosed in Hill et al., claim 10 is not anticipated by Hill et al.

Applicants have added new claims 15-24.

Applicants thank the Examiner for concluding that claims 1-5, 7, 8 and 11-14 are free of the prior art of record. Applicants advise the Examiner that Applicants mailed an Information Disclosure Statement on January 27, 2000, and Applicants request that the references cited therein be considered by the Examiner.